THE GEORGE INSTITUTE
for Global Health

Principles of analysis and reporting

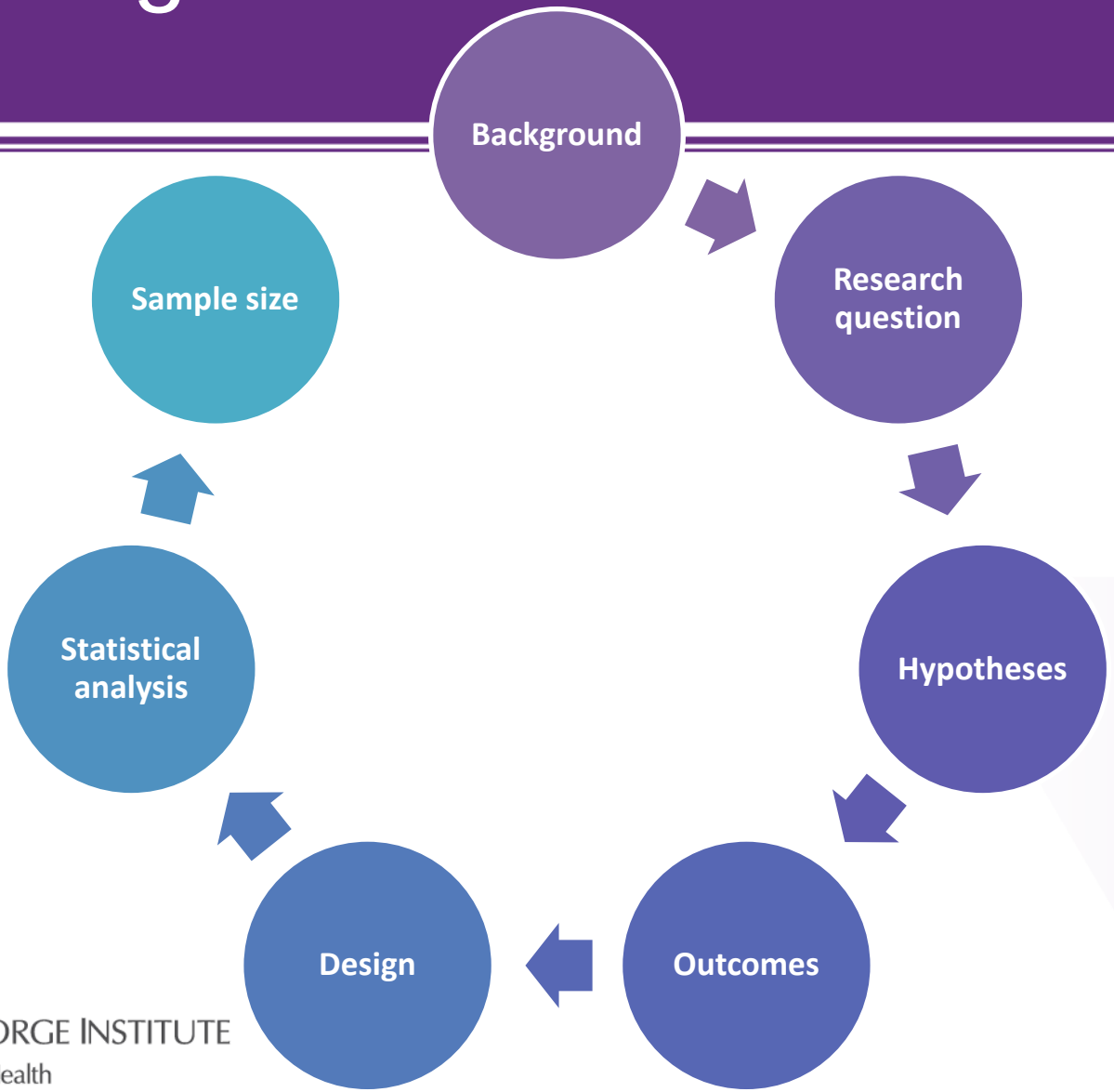
A/Prof Laurent Billot, MSc MRes AStat

Director, Statistics Division
The George Institute for Global Health

Principal Research Fellow
Sydney Medical School, University of Sydney

Australia | China | India | UK

Trial design



Protocol: key statistical elements

- Research question(s)
- Hypotheses to be tested
- Primary and secondary endpoints
- Design (parallel, factorial, cross-over)
- Timelines (including length of recruitment and follow-up)
- Sample size/Power for key endpoints
- Brief analysis plan
- Randomisation and blinding

Research rationale

Background: Why do we want to conduct this research?

- Important issue
- Potential solution
- Lack of existing evidence
- Impact and innovation

Hypotheses: What question(s) do we want to answer?

- Treatment A will decrease systolic blood pressure
- Treatment B will improve survival in patients with colon cancer

Background: example

1. **Issue**: Each year over 200 million major surgical procedures are performed globally. These surgeries can be associated with serious adverse medical outcomes such as cardiac death, myocardial infarction (MI) and stroke.
2. **Need**: Need for therapies that might reduce the risk of cardiovascular complications
3. **Solution**: Previous studies suggest that pre-operative statin therapy results in a reduction in clinically important post-operative events but data is limited
4. **Proposal**: Large placebo-control randomised trial

Hypothesis: example

- **Question**
  Daily administration of a cardiovascular polypill will lower SBP when compared to usual care
- **Outcome**
  Change in SBP between baseline and Month 12
- **H0**
  Average SBP Change in Polypill = Average SBP Change in Usual Care

Outcomes

- **Primary outcome(s)**
  - Recommend only one
  - At most two
  - The most important(s)
- **Secondary outcomes**
  - Key outcomes
  - Variation of primary outcome(s) e.g. Survival vs dichotomous
  - < 10
- **Others (tertiary/exploratory)**
  - Interesting but not very important
  - Do not really expect significant effect
- **Safety**

Outcomes: example

- **Primary outcome:** combined endpoint of death and disability as defined by the dichotomised "0-1" versus "2-6" cut-point on the modified Rankin Scale [mRS] at 3 months.
- **Secondary outcomes:**
  a) Symptomatic ICH based on NINDS criteria of Brain imaging (or necropsy) confirmed ICH with ≥1 points deterioration in NIHSS score or death within 36 hours from baseline
  b) Symptomatic ICH, defined by SITS-MOST criteria, as large ("type II") parenchymal ICH with ≥4 points decline in NIHSS score or death within 36 hours from baseline
  c) ICH of any type in Brain imaging ≤7 days of treatment;
  d) Death or disability by the alternative, but less widely used, shift analysis of scores on the mRS,
  e) Death,
  f) Disability,
  g) Neurological deterioration ≥4 points decline in NIHSS score over 72 hours,
  h) HRQoL by the EuroQoL
  i) Admission to residential care
  j) Health service use for calculation of resources and costs.

Sample size

- Power (at least 80%, preferably 90%)
- Type-I error rate (almost always 5%)
- Type of hypothesis (superiority or non-inferiority)
- Type of endpoint: continuous, dichotomous, time-to-event, etc
- Expected effect (i.e. difference between two treatments)
- Clustering
- Method of analysis
- Study duration
- Proportion non-adherent or lost to FU
- Interim analyses

Analysis

- **Continuous**
  - Example: Quality of life
  - Statistic: Mean
  - Analysis: T-test, Linear model
- **Dichotomous**
  - Example: Mortality at 90 days
  - Statistic: Proportion
  - Analysis: Chi-square, logistic regression
- **Ordinal**
  - Example: Modified Rankin
  - Statistic: Proportions, Mean
  - Analysis: Ordinal logistic regression
- **Count**
  - Example: Number of falls per year
  - Statistic: Rate
  - Analysis: Poisson regression
- **Survival**
  - Example: time to death
  - Risk or median time to event
  - Analysis: Log-rank test, Cox model

Sample size and analysis: example

- Outcome: % dead at 90 days
- Power = 90%
- Type-I error rate = 5%
- Expected mortality in control = 20%
- Expected mortality in active = 15%

  => absolute reduction = 15%-20% = -5%

  => relative reduction = 15%/20%=0.75
- Type of statistical analysis = Chi-square test
- Expected loss top FU = 10% in each arm
- Assuming no drop-outs/drop-ins
- **Sample size = 1418 / 90% = 1576**

Sample size and analysis: example

- Sample size

  A sample size of **1576** participants will provide **90** percent power (type-I error rate=**5%**) to test differences in mortality at 90 days. This is based on a mortality rate of **20%** in the control group (*Reference/justification*) and an expected mortality rate of **15%** in the active group (*Reference/justification*). The sample size allows for **10** percent of patients lost to follow-up (*Reference/justification*).

- Statistical analysis

  The primary analysis will be a chi-square test assessing the difference in mortality at 90 days. Adjusted analyses including stratification variables will be conducted using log-binomial regression. Survival analysis of time to death will be conducted as a secondary analysis using the log-rank test.

Randomisation

- Stratification (study centre, prognostic factors)
- Pre-specified list vs. dynamic allocation
- If pre-specified: reproducibility, blocks
- If dynamic: choice of algorithm (degree of randomness)
- Manual (i.e. envelopes) vs. electronic (i.e. IVRS or web-based)
- Integration with drug supply
- Procedures for emergency unblinding
- Storage and access

Ensure reproducibility
Independent validation

Blinding

- **Double-blind study**
  - Unblinded: IDMC statistician, IDMC members, IT
  - Blinded: everyone else
- **Open-label**
  - Unblinded: same as above + patients + personnel at site + those accessing database during study conduct (e.g. monitors)
  - Blinded: everyone else
- **Storage and access**
  - Store data on server
  - Avoid copies on hard drives
  - Restrict access

Randomisation and blinding: example

5B.3 Randomisation

Eligible participants will be randomly assigned to the polypill or usual care groups using a central randomisation service. The allocation sequence will be stratified by the presence or absence of established CVD and by investigator site.

Participants will be randomised to:

- Polypill based care

or

- Usual care (with usual cardiovascular medications)

5B.5 Blinding

Blinding of the participants to trial medication allocation will not be possible because the comparator is usual care. Therefore this is an open-label trial. However laboratory assessment of the cholesterol primary endpoint will be blind to group allocation. Bias from the unblinded measurement of blood pressure will be minimised by audited comparison of CRF entries with the memory values of an automated blood pressure-measuring device by the trial monitor. The results will be unblinded once the final statistical report has been completed.

Statistical analysis plan (SAP)

- Protocol synopsis
- Details of statistical methods/models to be used
- Analysis set (intent-to-treat vs. per-protocol)
- Multiplicity adjustments
- Possible covariate adjustments
- Handling missing data
- Sensitivity analyses
- Subgroup analyses
- Table shells and figure shells

Consider blind review
Publish or not publish?

SAP: example

UMPIRE

Use of a Multidrug Pill In Reducing Cardiovascular Events

STATISTICAL ANALYSIS PLAN

Final

Version 2.1

Adobe Acrobat Document

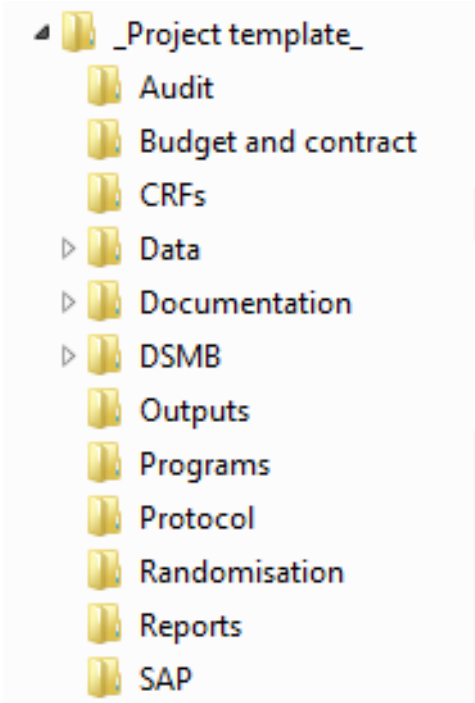
Reporting

- **Follow analysis plan**
  - Report everything
  - Indicate ad-hoc/exploratory analyses
- **Be explicit**
  - Methods
  - Covariate adjustments
  - Missing data handling
- **Interpret wisely**
  - Strength of results ($p=0.049 \neq p=0.0001$)
  - Multiplicity
  - Subgroups

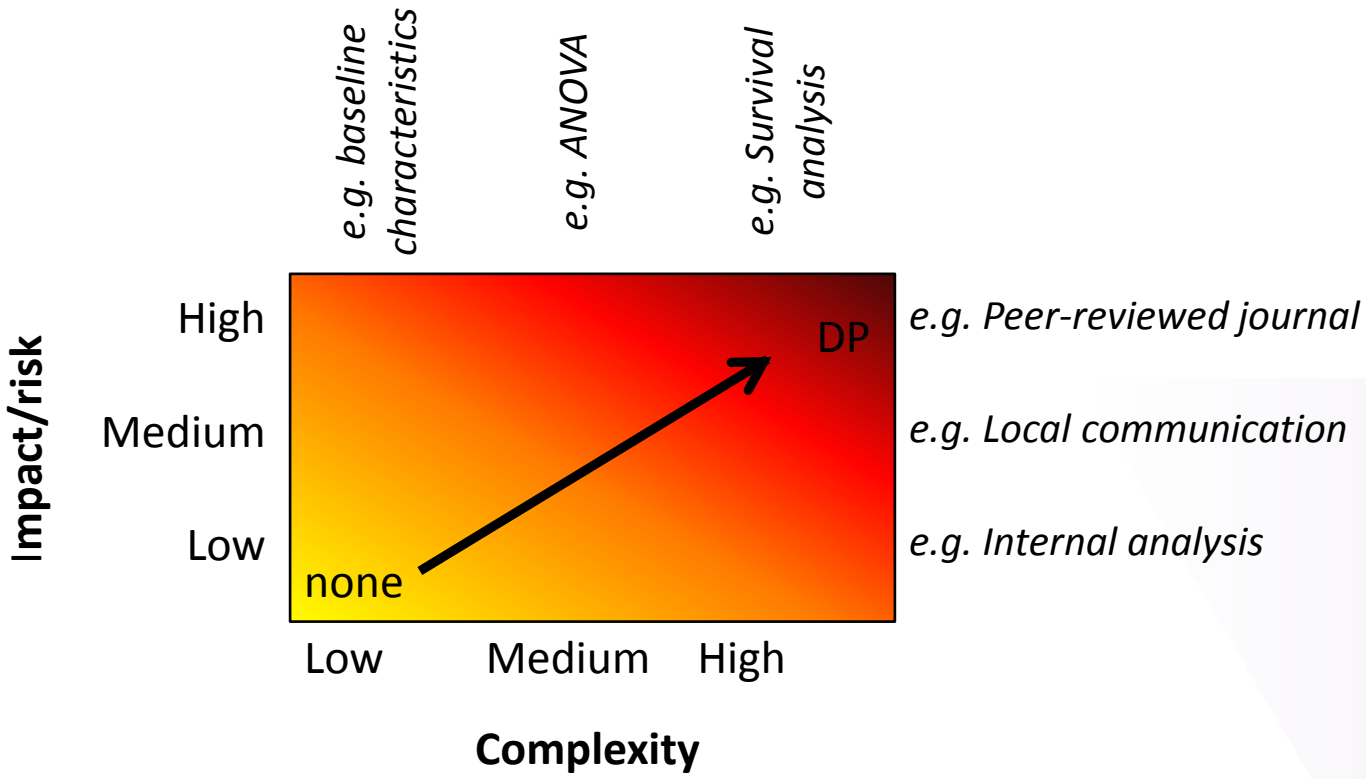
Traceability and Reproducibility

- **D-POP** trace

- Save code
- Use footnotes
- Version control
- Document (e.g. program header)
- Document more (e.g. program log)
- Use a consistent folder structure



Quality control



Summary

- Include key statistical aspects in protocol
- Clearly articulate background, hypotheses, design and outcomes
- Sample size calculation essential
- Pre-specify analyses in SAP
- Make sure analyses are reproducible
- Validate key results
- Report with transparency and moderation

THE GEORGE INSTITUTE
for Global Health

Thank you